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Rheumatoid factor in hypertension

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The rheumatoid factor, at a serum dilution of 1/16, was found to be present in 48 per cent of 29 severely hypertensive patients and in 18 per cent of 33 healthy normotensive blood donors, both groups being restricted to those aged between 40 and 60 years.

In both hypertensive patients and blood donors, the level of serum IgM did not significantly correlate with the presence of rheumatoid factor.

It is suggested that the rheumatoid factor appears as a result of vascular damage induced by hypertension.

Rheumatoid factor is a macroglobulin acting as an agglutinating antibody against denatured gammaglobulins and this may be a component of the host response to injury (Vaughan and Butler, 1962). Initially shown in patients with rheumatoid arthritis (Franklin *et al.*, 1957), it has subsequently been described in many other diseases involving chronic tissue damage, such as tuberculosis (Singer *et al.*, 1962), syphilis (Vaughan and Butler, 1962), subacute bacterial endocarditis (Williams and Kunkel, 1962), chronic liver diseases (Bonomo, LoSpalluto, and Ziff, 1963), scleroderma (Rothfield and Rodnan, 1968), ankylosing spondylitis (Sharp *et al.*, 1964), Still's disease (Torrigiani *et al.*, 1969), and in hypergammaglobulinaemic native tropical populations (Wells, 1967).

The rheumatoid factor thus appears to be associated with situations of chronic tissue damage and, therefore, the frequency of its occurrence becomes relevant to the study of the vascular injury which occurs in hypertension (Pickering, 1965). We report a survey of the incidence of rheumatoid factor in a group of severely hypertensive patients compared to normotensive blood donors.

Patients and methods

Consecutive patients attending the outpatient hypertension clinic or inpatients with a standing mean blood pressure (diastolic blood pressure plus a third of the pulse pressure) of 130 mmHg or more were selected, and, to minimize effects of age, only subjects between the ages of 40 and 60 years were included in this study. The majority of patients were referred to the clinic because of failed hypotensive therapy and, though a smaller number had never been treated, all patients had severe hypertension with standing blood pressure measured on three occasions over a period of three weeks. Patients with mild or episodic hypertension were not studied. Hypertensive patients with rheumatoid arthritis or any other condition known to be associated with an increased incidence of the rheumatoid factor were excluded. Healthy, consecutive blood donors, between the ages of 40 and 60 years, were used as controls. All blood donors had a standing systolic blood pressure of less than 150 mmHg and a standing diastolic blood pressure of less than 100 mmHg.

Rheumatoid factor was measured by a modified latex test slide technique (Singer and Plotz, 1956) using available reagents (RA test – Hyland Laboratories), and serum was heated to 56°C for 30 minutes before testing, so as to remove 'heat labile latex fixation factor' (Watson, 1965) which may give rise to false positive results. Serum IgM estimations were determined by the radial immunodiffusion technique (Fahey and McKelvey, 1965) using available immunodiffusion plates and protein standards (Hyland Laboratories).

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Results

Incidence of rheumatoid factor

Rheumatoid factor at a serum dilution of 1/16 was present in 14 out of 29 hypertensives (Table 1) and in 6 out of 33 blood donors (Table 2) and this difference is statistically significant ($\chi^2 = 17{\cdot}68$, $P < 0{\cdot}001$). The rheumatoid factor was present in 7 out of 16 male hypertensives and in 6 out of 29 male blood donors, and this difference is statistically significant ($\chi^2 = 5{\cdot}18$, $P < 0{\cdot}025$). There was an insufficient number of female blood donors aged 40 to 60 years to carry out a statistical analysis.

The average age of the hypertensive patients was 51·0 years, while that of the blood donors was 49·2 years. The average age of hypertensive patients with a demonstrable rheumatoid factor was 53·2 years, while that of blood donors with a demonstrable rheumatoid factor was 51·8 years. The average age of male hypertensive patients with demonstrable rheumatoid factor was 56·1 years, while that of male hypertensive patients without demonstrable rheumatoid factor was 48·4 years, and this difference is significant ($t=2·92$, $P<0·02$). The average age of female hypertensive patients with demonstrable rheumatoid factor was 50·3 years, while that of female hypertensive patients without demonstrable rheumatoid factor was 49·4 years, but this difference is not significant. The average age of male blood donors with demonstrable rheumatoid factor was 51·8 years while that of male blood donors without demonstrable rheumatoid factor was 49·0 years, and again this difference is not significant.

TABLE 1 *Age, sex, standing blood pressure, rheumatoid factor, and serum IgM of hypertensive patients*

Subject	*Age (yr)*	*Sex*	*Blood pressure* (mmHg)*	*Rheumatoid factor*	*Serum IgM (mg/100 ml)*
1	60	M	190/130	—	130
2	52	M	165/130	1/16	39
3	45	M	190/150	—	81
4	47	F	195/125	1/64	68
5	44	M	220/160	—	180
6	46	M	200/120	—	48
7	52	F	205/135	1/128	228
8	55	M	180/130	1/32	140
9	41	F	245/135	—	108
10	53	F	210/120	1/64	172
11	54	F	195/115	1/32	153
12	55	M	150/120	—	63
13	46	M	220/150	—	132
14	42	M	170/130	—	66
15	54	M	240/140	1/16	130
16	60	M	200/115	1/32	60
17	50	F	175/125	—	87
18	60	F	200/120	—	215
19	54	F	200/120	1/16	71
20	53	F	175/125	—	82
21	51	M	180/120	—	100
22	45	F	200/120	—	312
23	56	M	220/140	1/16	84
24	52	F	170/115	1/16	288
25	42	M	190/120	—	190
26	40	F	190/130	1/16	235
27	58	M	175/125	1/64	ND
28	58	M	190/120	1/256	ND
29	53	F	250/140	—	ND

ND = Not done.
* The standing blood pressure is the mean of two readings on the day the blood sample was collected.

TABLE 2 *Age, sex, rheumatoid factor, and serum IgM of blood donors*

Subject	*Age (yr)*	*Sex*	*Rheumatoid factor*	*Serum IgM (mg/100 ml)*
1	54	M	—	39
2	47	M	—	39
3	51	M	1/128	254
4	44	M	—	83
5	51	M	1/128	60
6	42	F	—	335
7	54	M	—	270
8	48	M	—	128
9	51	M	—	215
10	46	M	—	43
11	44	M	—	89
12	40	M	—	53
13	52	M	1/16	141
14	57	M	1/64	230
15	50	M	—	51
16	50	F	—	157
17	57	M	—	59
18	50	M	—	53
19	52	M	—	100
20	51	M	1/16	230
21	40	M	—	128
22	46	M	—	140
23	49	M	1/128	53
24	52	M	—	128
25	48	F	—	46
26	47	M	—	112
27	54	M	—	100
28	50	M	—	141
29	46	M	—	81
30	48	M	—	158
31	45	F	—	94
32	50	M	—	94
33	56	M	—	48

There was no significant association between type of hypertension (Table 3) and presence of rheumatoid factor. There was no significant difference in height of blood pressure between hypertensives with and without rheumatoid factor (Table 1).

Serum IgM and rheumatoid factor

The average serum IgM in hypertensives was 133·2 mg per 100 ml and average serum IgM in blood

TABLE 3 *Frequency of rheumatoid factor in different types of hypertensive patients*

Category	*Rheumatoid factor*		*Total*
	Present	*Absent*	
Essential hypertension	12	12	24
Malignant hypertension	1	2	3
Renal hypertension	1	1	2

TABLE 4 *Relation between rheumatoid factor and serum IgM*

Category	*Serum IgM: mean ± SE (mg/100 ml)*		*Statistical significance*
	Rheumatoid factor present	*Rheumatoid factor absent*	
Hypertensives	139·0 ± 23·0	128·1 ± 19·6	NS
Blood donors	161·3 ± 36·7	110·5 ± 13·7	NS
Combined: hypertensives and blood donors	146·4 ± 19·1		NS

donors was 119·8 mg per 100 ml, but this difference is not significant. There was not much difference in serum IgM between hypertensive patients having a demonstrable rheumatoid factor and those not having it (Table 4), and despite a slight trend towards increased serum IgM levels in blood donors having a demonstrable rheumatoid factor, again it was not significant. When hypertensives and blood donors were combined, average serum IgM in those having the rheumatoid factor was higher than in those not having it, but again this difference was not significant.

Discussion

Rheumatoid factor at a serum dilution in 1/16, was found in 48 per cent of severely hypertensive patients but in only 18 per cent of normotensive blood donors, both groups being aged between 40 and 60 years.

A small but definite percentage of normal subjects have detectable levels of rheumatoid factor varying from 4·5 per cent (Waller and Toone, 1968) to 20 per cent (Wells, 1967), but studies of population samples suggest that rheumatoid factor is a graded characteristic present to a certain extent in all subjects (Ball and Lawrence, 1961; Torrigiani and Roitt, 1967; Kellgren, 1969). Selection of a given titre as a minimal positive reaction is an arbitrary exercise which has to be carried out for each test system and which is further influenced by the population where the test is used as a diagnostic determinant. In patients with rheumatoid arthritis, latex fixation test and sheep cell agglutination test give reasonably concordant results (Kellgren, 1969); agglutination at a serum dilution of 1/16 is usually taken to indicate a positive response, and a similar criterion was adopted in this study.

The data presented here suggest an association between severe hypertension and presence of a demonstrable rheumatoid factor. A rheumatic disease survey carried out in the county of Tecumseh, Michigan, showed that when subjects were grouped by age into decades, prevalence of latex test positivity was related to systolic blood pressure, serum uric acid and serum cholesterol levels (Mikkelsen *et al.*, 1967). Furthermore, it was shown that occurrence of rheumatoid factor rose with age, and this has been confirmed by the work presented here and by other studies (Ghigliotti *et al.*, 1967). To minimize effect of age, only hypertensives and blood donors aged between 40 and 60 years were used in our study. Though subjects with a demonstrable rheumatoid factor tended to be older, this difference, except for male hypertensive patients, was not statistically significant. It is unlikely that increased incidence of rheumatoid factor in hypertensive patients is due to age alone.

Since the function of rheumatoid factor has not been elucidated for rheumatoid arthritis, one can only speculate as to its significance in hypertension. It is possible that the rheumatoid factor is an autoantibody to altered gamma-globulin (Normansell and Stanworth, 1968) and circulating rheumatoid factor gamma-globulin complexes have been described which exacerbate tissue injury (Cochrane, 1968). The role of rheumatoid factor thus appears to be to opsonize altered gamma-globulin and assist in its removal by the macrophages of the reticuloendothelial system. Some support for this comes from the observation that anti gamma-globulin antibodies appear in blood after acute tissue trauma such as cardiac surgery (Pretty *et al.*, 1968), and in rheumatoid arthritis and subacute bacterial endocarditis there is a positive correlation between presence of rheumatoid factor and raised levels of gamma-globulin (Messner *et al.*, 1968). If rheumatoid factor is an autoantibody to altered gamma-globulin or gamma-globulin complexes, then its appearance in hypertension is not surprising, since raised levels of serum IgG are also found in this condition (Ebringer and Doyle, 1970).

Serum IgM was found not to be significantly raised in patients or controls having a demonstrable rheumatoid factor. A similar situation occurs in sero-positive rheumatoid arthritis, where serum IgM is not significantly raised when compared to control subjects (Marcolongo *et al.*, 1967; Veys and Claessens, 1968) and a possible explanation for this may lie in the short half-life of serum IgM which is approximately 8 to 10 days (Kopp *et al.*, 1968). Increased rheumatoid factor activity could occur through increased metabolic turnover rather than an increase in the level of serum IgM, and this could be reflected in a decreased half-life for serum IgM, as has been described in some patients with rheumatoid arthritis (Levy *et al.*, 1969).

This study shows that rheumatoid factor becomes detectable in hypertension, a disease characterized by chronic vascular tissue damage. It is likely that rheumatoid factor appears after the onset of vascular injury, though the speed with which it develops is at present unknown.

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